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(21) International Application Number: PCT/HU93/00038 (22) International Filing Date: 17 June 1993 (17.06.93) (30) Priority data: P 92 02040 18 June 1992 (18.06.92) HU (71) Applicant (for all designated States except US): FABULON RG KOZMETIKAI KFT. [HU/HU]; Gyömrői út 12, H-1103 Budapest (HU). (72) Inventors; and (75) Inventors/Applicants (for US only) : HANGAY, György [HU/HU]; Rajk László u. 35-37, H-Budapest XIII (HU). KELEN, András [HU/HU]; Somfa köz 6, H-1106 Budapest (HU). KESERÜ, Péter [HU/HU]; Párkány u. 20, H-1138 Budapest (HU). DEMETER, Vodnár, János [HU/HU]; Rudnay Sándor tér 6, H-2500 Esztergom (HU). FRIEDMAN, Éva [HU/HU]; Fehérvári u. 147, H-1119 Budapest (HU). ALBERTI, Éva [HU/HU]; Hild József u. 2, H-2500 Esztergom (HU). KOVÁCS, György [HU/HU]; József u. 27, H-Budapest XVIII (HU). PUTZ, Pál [HU/HU]; Kun Béla ltp. 8/3, H-2500 Esztergom (HU). KARDICS, Izabella [HU/HU]; Bánomi ltp. 6, H-2500 Esztergom (HU).		(72) Inventor: MÉSZÁROS, Józsefné (deceased). (74) Agent: DANUBIA; Bajcsy Zsilinszky út 16, H-1051 Budapest (HU). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, JP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF INFLAMMATIONS AND DERMATOSSES INDUCED BY VIRUSES AND PROCESS FOR THE PREPARATION THEREOF (57) Abstract The invention relates to new cosmetic and/or medicinal compositions which beneficially affect virus-induced infections and inflammations of the skin and mucosa and promote the regeneration of the dermatoses caused, i.e. the compositions are able to restore the initial conditions of the skin.		

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COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF
INFLAMMATIONS AND DERMATOSES INDUCED BY VIRUSES AND
PROCESS FOR THE PREPARATION THEREOF

5 The invention relates to new cosmetic and/or
medicinal compositions which beneficially affect
virus-induced infections and inflammations of the
skin and mucosa and promote the regeneration of the
dermatoses caused, i.e. the compositions are able to
10 restore the initial conditions of the skin.

The compositions of the invention are special-
ly suitable for the treatment of infections and
dermatoses induced by herpes virus.

Several patents report on products suitable
15 for the treatment of herpes. The US patent
specification No. 3,179,766 recommends the hydrophilic
ointment tricontanol. Tricontanol (melissyl alcohol,
myricyl alcohol, $\text{CH}_3(\text{CH}_2)_{28}\text{CH}_2\text{OH}$) alleviates pain,
heals the wounds developing in acne and perioral
20 dermatitis, exerts antiinflammatory action and
restores the normal lipid content of the skin. In
the Swiss patent specification No. 005810 (CIBA) an
oral stick formulation containing heparin and
dissociating zinc salt are proposed. The Israeli
25 patent specification No. 065184 (see British patent
specification No. 029749 and US patent specification
No. 4,700,293, too) recommends a combination of
glycyrrhizin and steroids (e. g. triamcinolon) or
viricidal agents (e. g. idoxuridine). The first is
30 proposed for the treatment of aphtha with adjuvant
stomatitis while the latter one for oral, nasal or
genital herpes. The Roumanian patent specification
No. 098473 describes a mixture of poplar bud
extract, arnica blossom tincture and melilot oil.
35 The Hungarian patent specification No. 001224

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reports on antiherpetic 2'-chloro-2'-deoxyuridines substituted in position 5.

The cited patents also confirm that in this field of indication the use of natural substances is becoming popular world-wide, too. The present invention is also a representative of this trend of development, and is based on the observation that active ingredient concentrates can be prepared from particular natural substances by a specific process which can be used, alone or in combination, for the production of cosmetic agents or medicinal cosmetics of improved activity. Their activity can be further increased by applying adjuvants or specific formulations.

The invention relates to compositions of manifold application with viricide, antiinflammatory and regenerating activity wherein the concentrations of the ingredients given % by weight are as follows:

20	Glycyrrhizin, preferably in the form of sweet-root extract	0.005-0.4
	Rosemary acid, preferably in the form of plant extract	0.005-0.4
	Thyme oil (thymol content min. 20 %)	0.001-0.5
25	Allantoin	0-0.5
	Polydocanol	0-5.0
	α -Bisabolol	0.005-0.5
	Soluble collagen	0.001-0.05
	Irgasan OP 300	0-0.5
30	Ethanol	0-90.

The compositions may contain further carriers, additives and auxiliary materials usually applied in the preparation of cosmetic or medicinal compositions, preferably water, propyleneglycol, acrylamide-sodium acrylate copolymer, PEG-7,

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glycerol cocoate and isooctyl nonanoate, as well as solubilizing agents, lipids, preservatives and fragrance components in hydrogel, lotion-ointment, liquid emulsion, spray, stick or drop formulation.

5 As regards the constituents of the composition it is known from literature sources that rosemary acid (caffeoyl- α -hydroxy-dihydrocaffeic acid), together with quinic acid, chlorogenic acid and caffeic acid, is present in plants of the labiate family (Laminaceae), mainly in *Melissa*
10 *officinalis*, *Hyssopus officinalis*, *Rosmarinus officinalis* and *Salvia officinalis*. Its virostatic, antibacterial and antimycotic potency is reported by I. K. Heimann and W. Schultze in the *Zeitschrift für Phytotherapie* Sept. 1988, 82-83.

15 Because of their sweet taste the sweet root (*Glycyrrhiza glabra*) extracts are used as sweeteners to improve taste and as expectorants (B. Issekutz: (Drug prescription, *Gyógyszerrendelés* p. 600 *Medicina*, Budapest, 1979). The regular use of standard preparations may reduce
20 the increased tension of the stomach wall and the inflammation of gastric mucosa (Gizella Verzár Petri: *Gyógynövények a gyógyászatban* (Medicinal plants in therapy), p. 92, *Medicina*, Budapest, 1984). Soviet authors [I. A. Murajev 25 et al.: *Farmacia* (Moscow), 94 (2), 84,
25 1979] found it to be more or less equiactive with prednisolone in contact allergy and dermatitis. Glycyrrhizin, the major constituent of sweet root has mineralocorticoid, antiinflammatory, antiedema and epithelizing (wound healing) properties.

30 The volatile oil of thyme (*Thymus vulgaris*) contains mainly thymol, carvacrol, p-cymol, furthermore linalool, borneol, geraniol and β -pinene. Due to its thymol content the thyme oil has viricide effect and inhibits a major part of wound
35 bacteria even at 3000fold dilution (Gizella Verzár

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Petri: Medicinal plants in therapy, Medicina, Budapest, 1984, p. 74.).

The α -bisabolol is one of the major components of camomile (*Matricaria chamomilla*). Primarily it
5 has antiinflammatory effect and promotes granulation.

The allantoin promotes the skin-regeneration and hydration.

The collagens, which can be found in the skin, also play role in hydration, but based on other
10 mechanism.

The polydocanol is ingredient of numerous medicinal and cosmetic composition. It has analgetic and local anaesthetic effect.

According to the literature individual compo-
15 nents of the preparation of the present invention are applied, though with varying frequency, in medical practice, but no preparation which has similar composition as that of the invention and is produced with a process similar to the disclosed
20 one. The product(s) are highly potent, have a broad spectrum of activity and promote the rapid and full regeneration of the affected skin areas.

The preparation of individual medicinal plant extracts, used in the preparation, as well as the
25 composition of the compositions are summed up as follows:

Characterization of components:

1.) Dry extract with rosemary acid content:

An aqueous alcohol (methanol, ethanol, iso-
30 propanol) extract is prepared from the leaves of a plant from Laminaceae family, e.g. rosemary, melilot (*Melissa officinalis*), *Salvia officinalis* and *Hyssopus officinalis*, etc. After removing the solvent the residue is acidified to pH 2-3 with an
35 inorganic acid, the mixture is extracted with a

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water immiscible solvent (ether, chloroform, dichloromethane, ethyl acetate, etc.), the layers are separated and the solvent is removed from the organic layer yielding a dry extract.

5

2.) Dry extract containing glycyrrhizin:

The sweet root is extracted with water or aqueous alcohol (methanol, ethanol, isopropanol) and the solvent is removed. The aqueous solution is
10 acidified to pH 2-3 with an inorganic acid, the precipitated mixture is filtered, the precipitate is dried, dissolved in ethanol, the pH of the solution is adjusted to 7-8 with ammonia, filtered and evaporated to dryness.

15 3.) Thyme oil. Aetheroleum thymi (Hungarian Pharmacopoea No. 7.)

Purified volatile oil prepared from the blossoming, fresh branch tops of the garden thyme (Thymus vulgaris) with steam distillation. The
20 product has a phenol content not less than 20.0 % (v/w) expressed in thymol.

The examination of the effect of the compositions:

The product is specifically beneficial for symptoms
25 of the mucosa (oral and genital) induced by herpes simplex virus. Applied in the early stage the development of erythema and edema is suppressed and recovery is accelerated. In recurrent cases, applied before the development of symptoms, superinfection is fully inhibited.
30 bited. Furthermore, subjective symptoms, such as itching and stretching, are alleviated, and recovery is rapid and traceless. The skin becomes refreshed and hydrated.

Two figures are shown to demonstrate the efficacy of the product. Figure 1 presents the results of the comparative study of the preparation of the invention (herpes
35

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gel prepared according to procedure 1) and that of the commercial control products, together with the duration of recovery of untreated cases. The following control preparations were tested in the study (Figure 1 shows the mean values of the results obtained):

1.) Medicinal gel and paint formulation containing the extract of 15 % (w/w) *Chelidonium herba*, 3 % (w/w) *Menthae piperita folium*, 1 % (w/w) *Calendula officinalis*, 2 % (w/w) *Thymi herba* and 2 % (w/w) *Millefolii herba*, prepared with 50 % (w/w) ethanol.

2.) Medicinal suspension ointment formulation containing 0.8 % (w/w) of 3-(2-deoxy-D-ribofuranosyl)-5-isopropyluracil.

3.) Medicinal alcoholic gel formulation containing 0.2 % (w/w) *primicium sulfuricum* and 2 % (w/w) *lidocain*.

4.) Painting agent containing 0.5 % (w/w) of zinc sulfate widely used in magistral preparations.

The compositions according to the invention reduced the duration of symptom free recovery by 3-4 days compared to the control products and by 7-9 days compared to the untreated control cases. Figure 2 presents the distribution of major recovery categories in the case of the preparation of the invention. According to the chart in about 30 % of the subjects crusts or blisters failed to develop and symptoms were eliminated within 2 days. In about 60 % of the patients only a thin and flexible crust was formed and wound healing was accelerated. Finally in about 10 % of the cases the rate of recovery, both as regards symptoms and wound healing, was similar to that observed with the control preparations. Further observations confirmed that in the case of herpes simplex infections the

product prolonged the interval elapsing till the recurrence of the disease. The symptom free periods may even increase from one to two weeks to 2 months.

From the tests performed the diagram of the hydrating effect of the gel containing the entire active ingredient combination, taken with a SKIN Resistance Meter, is shown in Figure 3.

Preferred formulations of the preparations according to the invention are listed as follows:

In the major part of indications the most advantageous formulation proved to be the rapidly absorbing and penetrating gel form which is easy to handle. The formulations specified (1-3) are partly usual gels and partly microemulsions [values in the table are expressed in % by weight (w/w)]:

<u>Herpes gel formulations</u>			
	1	2	3
Acrylic acid/Na acrylate			
copolymer (Hostacerin PN 73)	2.0	1.5	
POE(45) hydrogenated ricinol			
acid triglyceride			
(Cremophor RH 40)	2.0	1.5	
POE(7) glycerol cocoate			
(Cetiol HE)	2.0	5.0	
Isooctadecyl isononanoate			
(PCL liquid)	2.0	0.3	
Propyleneglycol	8.0	10.0	12.0
Ethanol	30.0	30.0	16.0
POE(9) lauryl alcohol			
(Polidokanol)	2.0	1.0	2.0
Polyoxyethylene/polyoxypropylene block polymer			
(Lutrol FC 127)			19.0
Allantoin	0.1	0.2	
α -Bisabolol	0.1	0.05	0.1
1 w/w % Collagen solution	0.5	1.0	0.5

	Triclosan (Irgasan OP 300)	0.1	0.1	
	Glycyrrhizin	0.1	0.2	0.15
	Rosemary acid	0.1	0.2	0.15
	Thyme oil	0.02	0.025	0.02
5	Distilled water	ad	100	100

The gels are prepared by dissolving allantoin in the bulk of water, then in some cases (formulations 1-10 2) also the copolymer, using slow stirring.

Polydocanol, and in some cases (formulations 1-2) also Irgasan, are dissolved in part of the alcohol. The remaining volumes of alcohol and water are combined and the formerly solubilized thyme oil is added to the 15 mixture. The phases are stirred at low r. p. m., then the lipid additives are poured to the mixture under stirring in the following order: solution of rosemary acid and glycyrrhizin in propyleneglycol and solution of α -bisabolol and collagen. After the addition 20 stirring is continued for further 5-10 minutes. Ointment is also a formulation of choice, see formulations 4 to 6 [values in the table are expressed in % by weight (w/w)]:

25	<u>Herpes ointment formulations</u>	<u>4</u>	<u>5</u>	<u>6</u>
	Liquid paraffin	18.0	18.0	20.0
	Stearin	7.0	8.0	9.0
	Polyoxyethylene fatty acid ester	6.0	7.0	8.0
30	Isooctyl stearate	4.0	3.0	3.0
	Propyleneglycol	4.0	7.5	12.0
	POE-9 lauryl alcohol (polydocanol)		1.0	2.0
	Allantoin	0.1	0.1	0.2
35	α -Bisabolol	0.1	0.15	0.05

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	1 w/w % Collagen solution	0.5	0.5	1.0
	Triclosan (Irgasan DP 300)		0.1	0.1
	Glycyrrhizin	0.05	0.1	0.2
	Rosemary acid	0.05	0.1	0.2
5	Thyme oil	0.03	0.04	0.05
	Distilled water	ad	100	100
			100	100

Ointments are prepared by melting the lipid components and the emulsifier - liquid paraffin, stearin, isooctyl stearate or polyoxyethylene (POE) fatty acid ester, resp. - and heating the mixture to about 70°C. Thereafter the polydocanol is added, and, if desired (formulations 5 and 6), Irgasan. Allantoin is dissolved in water then the aqueous phase is heated to about 70°C.

15 After completed homogenization, under steady cooling and moderate stirring, at about 60°C the solutions of rosemary acid and glycyrrhizin in propyleneglycol, solutions of α -bisabolol and collagen, then at temperatures lower than 50°C thyme oil are added. Stirring is continued till the mixture becomes cool (about 30°C).

Alcoholic paint, drop or spray are also formulations of choice. The composition of formulations 7 to 9 are listed in the following.

25

<u>Herpes formulations</u>		7	8	9
	Ethanol	20.0	30.0	
	Propylene glycol	5.0	8.0	40.0
	POE(45) hydrogenated ricinol			
30	acid triglyceride			
	(Cremophor RH 40)	1.0	2.0	3.0
	Triclosan (Irgasan OP 300)	0.05	0.1	
	Allantoin	0.05	0.1	0.2
	α -Bisabolol	0.05	0.2	0.1
35	1 w/w % Collagen solution	1.0	0.5	0.5

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Glycyrrhizin		0.05	0.1	0.2
Rosemary acid		0.05	0.1	0.2
Thyme oil		0.02	0.05	0.05
Distilled water	ad	100	100	100

5

The solutions are prepared by solubilizing first the thyme oil, preferably with POE(45) hydrogenated ricinol acid triglyceride. Irgasan is dissolved in 10 alcohol, and allantoin in the bulk of water. The phases prepared in this way are mixed, then, under constant stirring the solution of α -bisabolol and collagen (formulations 7 and 8) is added to the system, finally the propyleneglycol solution of 15 glycyrrhizin and rosemary acid. Stirring is continued for a couple of minutes after the addition.

Alcoholic painting composition and aerosol foam or spray composition using an appropriate carrier gas can be also prepared.

What we claim is

5

1. Compositions for the treatment and prophylaxis of inflammations and dermatoses of the skin induced by viruses characterized in that containing ingredients given in % by weight as

10 follows:

	Glycyrrhizin	0.005-0.4
	Rosemary acid	0.005-0.4
	Thyme oil (thymol content min. 20 %)	0.001-0.5
	Allantoin	0-0.5
15	Polydocanol	0-5.0
	α -Bisabolol	0.005-0.5
	Soluble collagen	0.001-0.05
	Irgasan OP 300	0-0.5
	Ethanol	0-90

20 furthermore auxiliary materials usually applied in the preparation of cosmetic and medicinal compositions.

2. Compositions as claimed in claim 1 characterized in that containing as auxiliary materials water, propyleneglycol, acrylamide/sodium
25 acrylate copolymer, PEG-7-glyceryl cocoate, isooctyl nonanoate, solubilizing agents, lipids and preservatives.

3. Compositions as claimed in either of claims 1 or 2 for the treatment and prophylaxis of viral infections and inflammations characterized in that the composition
30 is formulated as a liquid, drop, aerosol, foam, ointment, emulsion or gel formulation.

4. A process for preparing compositions suitable for the treatment and prophylaxis of inflammations and dermatoses of the skin induced by viruses which comprises
35 mixing the ingredients given in % by weight as follows:

	Glycyrrhizin	0.005-0.4
	Rosemary acid	0.005-0.4
	Thyme oil (thymol content min. 20 %)	0.001-0.5
5	Allantoin	0-0.5
	Polydocanol	0-5.0
	α -Bisabolol	0.005-0.5
	Soluble collagen	0.001-0.05
	Irgasan OP 300	0-0.5
10	Ethanol	0-90

furthermore auxiliary materials usually applied in the preparation of cosmetic and medicinal composition and converting them to cosmetic or medicinal compositions.

5. A process as claimed in claim 4 which
 15 comprises using water, propyleneglycol, acrylamide sodium acrylate copolymer, PEG-7-glyceryl cocoate, isooctyl nonanoate furthermore solubilizing agents, lipids and preservatives as auxiliary materials.

6. A process as claimed in either of the claims
 20 4 or 5 which comprises converting the compositions to liquid, drop, aerosol, foam, ointment, emulsion or gel formulations.

7. Therapeutic process for the treatment and prophylaxis of infections, inflammations and
 25 dermatoses of the skin and mucosa induced by viruses which comprises treating the infected body surface or the surface susceptible to infection with an effective dose of the preparation containing ingredients given in % by weight as follows:

30	Glycyrrhizin	0.005-0.4
	Rosemary acid	0.005-0.4
	Thyme oil (thymol content min. 20 %)	0.001-0.5
	Allantoin	0-0.5
	Polydocanol	0-5.0
35	α -Bisabolol	0.005-0.5

Soluble collagen

0.001-0.05

Irgasan OP 300

0-0.5

Ethanol

0-90

furthermore auxiliary materials usually applied in the
5 preparation of cosmetic and medicinal composition.

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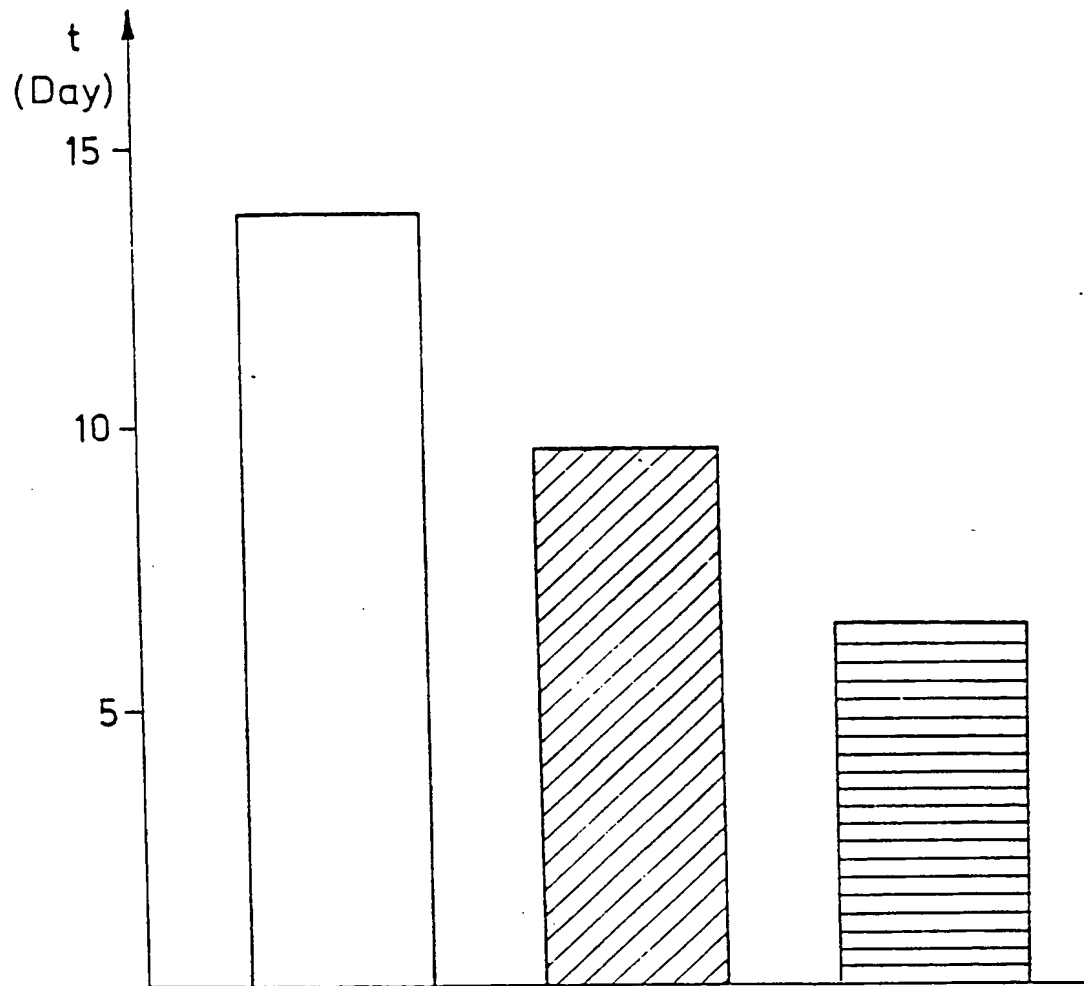


Fig.1

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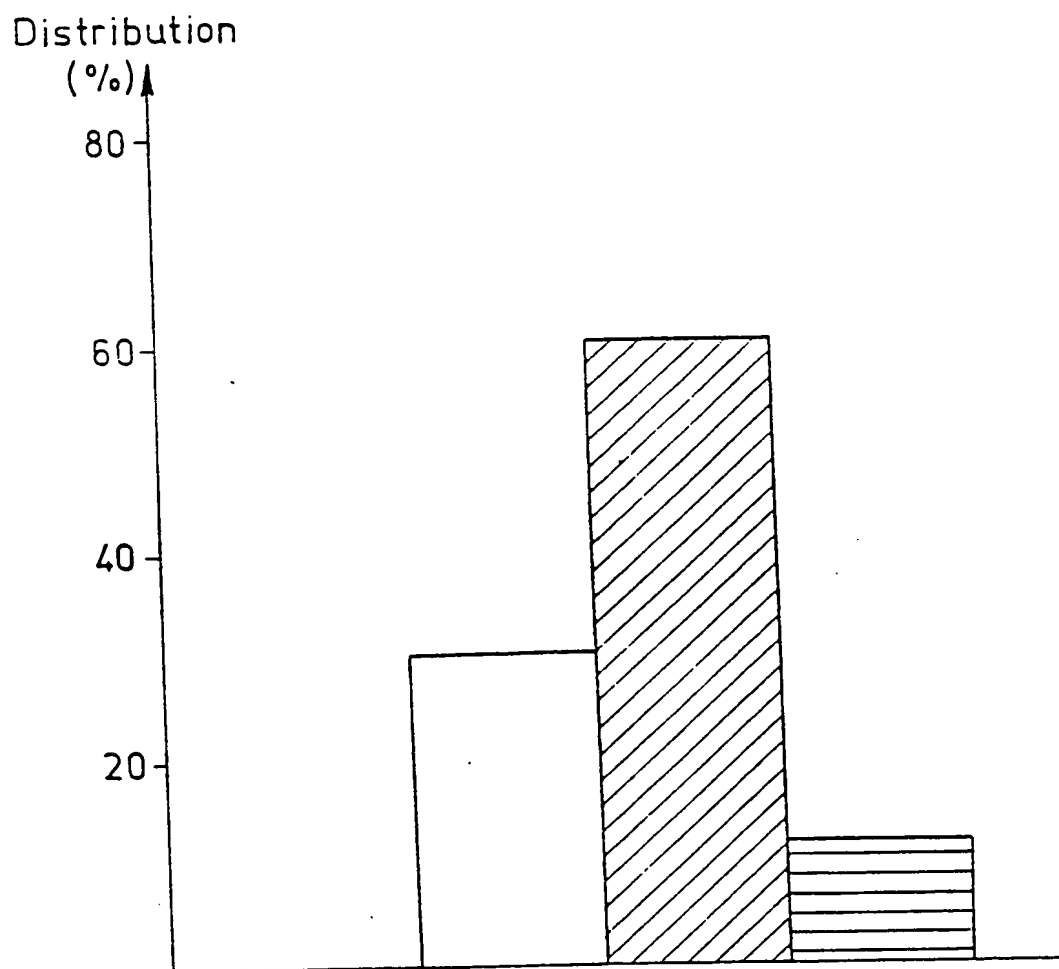


Fig. 2

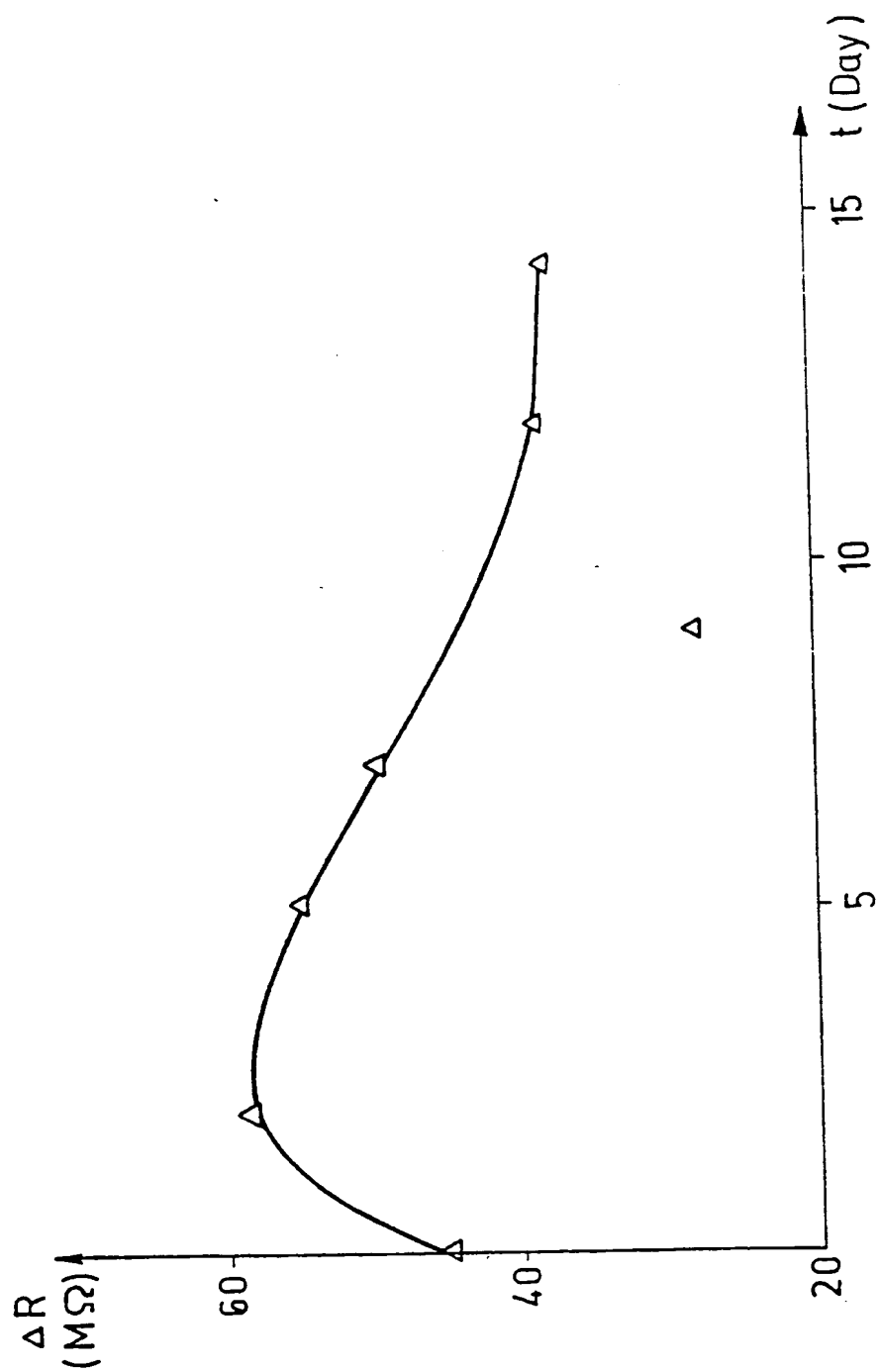


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 93/00038

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Patent Abstracts of Japan, unexamined applications Section C, Volume 16, no. 20, issued 1992, January 20, The Patent Office Japanese Government, page 17 C 902, the abstract no. 03-236 323 (KOBAYASHI KOSE CO LTD)..	1
A	Patent Abstracts of Japan, unexamined applications, Section C, Volume 16, no. 207, issued 1992, May 18, The Patent Office Japanese Government, page 23 C 941, the abstract no. 04-36 215 (SUNSTAR INC).	1
A	FR, A1, 2 614 787 (POLA KASEI KOGYO KABUSHIKI KAISHA) 10 November 1988 (10.11.88), claims 1,2,5. -----	1,5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 93/00038

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵: A 61 K 31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵: A 61 K 31/70

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, WPIL; glycyrrhizin?
glycyrrhizinic w acid) skin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB, A, 2 167 296 (YISSUM RESEARCH AND DEVELOPEMENT COMPANY OF THE HEWBREW UNIVERSITY OF JERUSAMLEM) 29 May 1986 (29.05.86), pages 3,4, examples 8-12.	1,7
A	EP, A1, 0 487 404 (KABUSHIKI KAISHA HAYASHIBARA SEIBUTSU KAGAKU KENKYUJO) 27 May 1992 (27.05.92), claim 6.	1
A	GB, A, 2 071 494 (KANEBO LTD. & MARUZEN KASEI CO. LTD.) 23 September 1981 (23.09.81), abstract.	1
A	Patent Abstracts of Japan, unexamined applications, Section C, Volume 8, no. 98, issued 1984, May 09, The Patent Office Japanese Government, page 101 C 221, the abstract no. 59-13 716 (RAION K.K.).	1
A	Patent Abstracts of Japan, unexamined applications, Section C, Volume 12, no. 467, issued 1988, December 07, The Patent Office Japanese Government, page 120 C 550, the abstract no. 63-188 628 (SHISEIDO CO.)	1

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT
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